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STEREOSELECTIVE SYNTHESIS OF OPTICALLY PURE β,γ-UNSATURATED α-AMINO ACIDS IN BOTH L AND D CONFIGURATIONS

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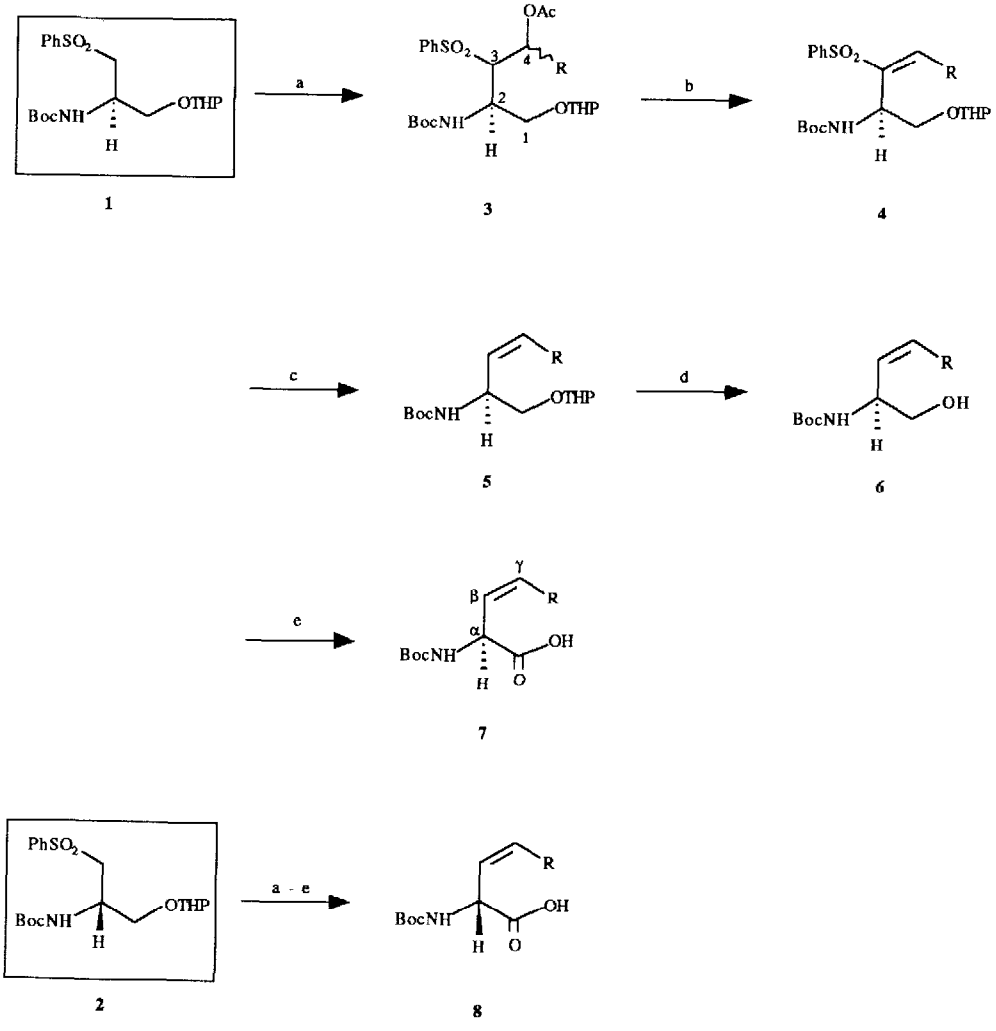
Summary : A new method for the stereoselective synthesis of optically pure β,γ-unsaturated α-amino acids in L or D configuration is developed by reacting the dilithiate of (2R)-2-Boc-amino-3-phenylsulfonyl-1-(2-tetrahydropyranyloxy)propane **1** or its (2S)-antipode **2**, both derived from L-serine, with aldehyde, followed by stereoselective olefin formation, desulfonylation and oxidation.

It has been reported that naturally occuring β,γ-unsaturated α-amino acids possess antibiotic activity and enzyme inhibitory properties (1). In particular, since the generalization by Rando that β,γ-unsaturated α-amino acids act as "suicide" substrates for pyridoxal phosphate dependent enzyme (2), several synthetic analogs have been developed as specific irreversible inhibitors of these enzymes (3). Hence, this class of α-amino acids holds high biological interest. However, establishing a general method for their preparation poses a considerable synthetic challenge. Though the synthesis of optically active vinyl glycine, the simplest β,γ-unsaturated α-amino acid, is established (4), thus far most of the methods developed for more complex ones still lack in general applicability, stereoselectivity and optical purity of the resulting amino acids (5).

In this communication, we describe a new approach to the stereoselective synthesis of optically pure β,γ-unsaturated α-amino acids in both L and D configurations. The key intermediates in our method are (2R)-2-Boc-amino-3-phenylsulfonyl-1-(2-tetrahydropyranyloxy)propane **1** and its (2S)-antipode **2** which we prepared from N-Boc-L-serine methylester and subsequently converted to optically pure non protein L- and D-α-amino acids, respectively (6). In conjunction with our ongoing effort to expand this new synthetic approach, we assumed that compounds **1** and **2**, coupled with Julia's method for stereoselective olefin synthesis (7), can be suitable starting materials for the synthesis of optically pure β,γ-unsaturated α-amino acids with desired α carbon configuration and substituents on β, γ carbons.

In order to explore the feasibility of this methodology, we chose N-Boc protected L-Z-propenylglycine **7** (R = Me) reported as an irreversible inhibitor of microbial methionine γ-lyase (3b), and its D-isomer **8** (R = Me) as model compounds. The synthetic route is outlined in the following Scheme.



1 3 4 5 6 7 2 8

(a) 2 equiv n-BuLi/THF, 2 equiv RCHO (R = Me), -78°C, 1 h ; 1.2 equiv Ac_2O, 0°C, 30 min ; (b) 3 equiv powdered NaOH/diethylether, powdered molecular sieves (3 Å), 2 h ; (c) 6 equiv $Na_2S_2O_4$, 12 equiv $NaHCO_3$, 50% aqueous EtOH, reflux, 3 h ; (d) EtOH-cat.PyH.OTs, 60°C, 6 h ; (e) 6 equiv PDC/DMF, 25°C, 6 h.

Scheme

Treatment of the dilithiate of **1** with RCHO (R = Me) at -78°C followed by acetylation in situ afforded the acetoxy sulfone **3** (8). Vigorous stirring of **3** in dry diethylether in the presence of powdered NaOH and thoroughly dried molecular sieves (3 Å, 80 mg/mmol) gave, after rapid filtration of the reagents and concentration of the eluents, the E-vinylsulfone **4** (9). In accord with the result by Julia (7a), we obtained exclusively the E-isomer which can be purified by flash chromatography (n-hexane/EtOAc = 1/1). Reductive desulfonylation of **4** was performed by refluxing the crude reaction mixture with sodium dithionite in the presence of sodium bicarbonate in 50% aqueous ethanol. Purification by flash chromatography (n-hexane/EtOAc = 3/1) furnished the Z-olefin **5** (10) in 43% yield (in 3 steps from **1**) and concomitantly unreacted starting material **1** (12%). Removal of THP from **5** afforded the amino alcohol **6**, $[\alpha]_D^{20}$ - 29° (c 1,5, MeOH), mp 48-49°C, in quantitative yield (11). Oxidation of **6** with PDC in DMF was accomplished in 6 h, in 55% yield. The usual extraction procedure for the purification of carboxylic acid derivatives facilitated the removal of unreacted starting material and unidentified by-products, and double bond migration is not observed. This yielded N-Boc-L-Z-propenylglycine **7** (12) as a viscous oil, $[\alpha]_D^{20}$ + 103° (c 2, MeOH), mp 138-140°C (dicyclohexylamine salt). Proceeding in the same manner as with **1**, compound **2** afforded N-Boc-D-Z-propenylglycine **8** : viscous oil, $[\alpha]_D^{20}$ -102° (c 2, MeOH), mp 138-140°C (DCHA salt).

The optical purity of **7** and **8** was established as ≥ 97% by ^1H NMR analysis of the (+)-α-methoxy-α-trifluoromethylphenylacetyl derivatives at 400 MHz (13).

Our preliminary results clearly demonstrate that the compounds **1** and **2** can serve as suitable starting materials for the stereoselective synthesis of optically pure β,γ-unsaturated α-amino acids in both L and D configurations, respectively. In addition, some of the intermediate products of this 5-step synthetic strategy can be used as starting materials from which to build novel compounds. Further studies in the application of the present approach are currently under investigation.

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8. ^{1}H NMR : δ (200 MHz, $CDCl_3$) 8.05-7.70 (2H, m, Ar-H), 7.65-7.31 (3H, m, Ar-H), 5.83-5.20 (2H, m, NH, 2-H), 4.79-4.29 (2H, m, OCHO, 3-H), 4.18-3.32 (5H, m, 2 x CH_2O, 4-H), 2.11 (3H, s, OAc), 1.93-1.14 (9H, m, $(CH_2)_3$, CH_3), 1.48 (9H, s, Boc). EIMS : m/z 486.

9. IR ($CHCl_3$) : 3430, 1700, 1490, 1350, 1155, 1130 cm^{-1}. ^{1}H NMR : δ (200 MHZ, $CDCl_3$) 8.00-7.80 (2H, m, Ar-H), 7.73-7.40 (3H, m, Ar-H), 7.10 (1H, m, 4-H), 5.60-4.90 (2H, m, NH, 2-H), 4.60-4.32 (1H, m, OCHO), 4.00-3.35 (4H, m, 2 x CH_2O), 2.03 (3H, br d, J = 7 Hz, CH_3), 1.90-1.38 (6H, m, $(CH_2)_3$), 1.25 (9H, s, Boc). EIMS : m/z 426.

10. IR ($CHCl_3$) : 3440, 1700, 1485, 1415 cm^{-1}, ^{1}H NMR : δ (200 MHz, $CDCl_3$) 5.82-5.30 (2H, m, 3-, 4-H), 4.93 (1H, br, NH), 4.67 (2H, m, 2-H, OCHO), 4.03-3.31 (4H, m, 2 x CH_2O), 1.98-1.48 (6H, m, $(CH_2)_3$), 1.75 (3H, br d, J = 6 Hz, CH_3), 1.45 (9H, s, Boc). EIMS : m/z 286.

11. IR ($CHCl_3$) : 3430, 1695, 1480, 1385, 1360, 1155 cm^{-1}. ^{1}H NMR : δ (200 MHz, $CDCl_3$) 5.93 (1H, br dq, J = 10, 7 Hz, 4-H), 5.53 (1H, br tq, J = 10, 6 Hz, 3-H), 4.95 (1H, br, NH), 4.70 (1H, br quint., J = 6 Hz, 2-H), 3.76 (2H, d, J = 6 Hz, 1-H_2), 1.80 (3H, br d, J = 7 Hz, CH_3), 1.52 (9H, s, Boc). EIMS : m/z 202.

12. IR ($CHCl_3$) : of methyl ester after treatment of **7** with CH_2N_2 3430, 1735, 1700, 1490, 1480 cm^{-1} ^{1}H NMR of methyl ester : δ (200 MHz, $CDCl_3$) 5.75 (1H, dq, J = 10, 7 Hz, γ-H), 5.24 (1H, tq, J = 10, 2 Hz, β-H), 5.50-4.64 (2H, m, NH, α-H), 3.67 (3H, s, OCH_3), 1.81 (3H, dd, J = 7, 2 Hz, CH_3), 1.46 (9H, s, Boc).

13. ^{1}H NMR of N-(+)-α-methoxy-α-trifluoromethylphenylacetyl-L-Z-propenylglycine methylester : δ (400 MHz, $CDCl_3$) 3.75 (3H, s, $COOCH_3$), 3.38 (3H, s, OCH_3), 1.83 (3H, br d, J = 7 Hz, CH_3). D isomer : δ (400 MHz, $CDCl_3$) 3.78 (3H, s, $COOCH_3$), 3.53 (3H, s, OCH_3), 1.79 (3H, br d, J = 7 Hz, CH_3).

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